REMARKS

Claims 20 and 22 have been amended. No new matter is added by the amendments, and support may be found throughout the specification, including at page 8, lines 22-25; page 11, line 27 through page 12, line 7. Claim 44, withdrawn by the Examiner as directed to a nonelected invention, has been cancelled without prejudice or disclaimer. Claims 20, 22-23, 25-31, 33-34, 36, and 40-43 are pending in the application. Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Withdrawn Rejections

Applicants acknowledge the withdrawal of the rejection of claims 17, 21, 23, 25-29, 34-35, and 39 as anticipated by Cleland, as well as the withdrawal of the rejection of claims 17, 21, 23, 25-28, 34, and 39 as anticipated by Suzuki.

Applicants also acknowledge the withdrawal of the rejection of claims 17, 20-21, 23, 25-29, 34-35, and 39 as obvious over Cleland in view of the syringe section (page T515) Aldrich catalog.

35 U.S.C. 102

Claims 20, 22, 28, 30-31, and 40-43 were rejected under 35 U.S.C. 102(b) as anticipated by Tsunenaga. Applicants traverse this rejection.

Amended independent claim 20 recites a method for administering a biologically active agent, comprising injecting a formulation comprising hyaluronic acid (HA) dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent weight by volume, and particles comprising a first component that is a biologically active agent and a second component that is a biocompatible polymeric matrix.

Amended independent claim 22 recites an injectable formulation comprising hyaluronic acid dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent weight by volume, and particles comprising a first component that is a biologically active agent and a second component that is a biocompatible polymeric matrix.

Applicants note that "[a] claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."

MPEP 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

In light of the foregoing standard, Applicants assert that Tsunenaga does not disclose each and every element of the pending claims. Specifically, Tsunenaga does not disclose an injectable formulation comprising particles having a biologically active agent and a biocompatible polymeric matrix, wherein the biologically active agent and the biocompatible polymeric matrix are separate components.

Rather, Tsunenaga discloses an aqueous solution or dispersion of collagen in hyaluronic acid for injection (column 2, lines 52-68). Tsunenaga discloses that the aqueous collagen solution or dispersion can be used "as an agent for correction and reparation of depressed parts or void areas of soft tissue" (column 5, lines 60-64), since the collagen can regenerate collagen fibers, and the hyaluronic acid can inhibit the absorption of collagen after injection (column 10, lines 57-59). Therefore, the particles of Tsunenaga only comprise a single component (collagen).

The Examiner asserts that collagen is both a biologically active agent and a biocompatible polymeric matrix. Even if the Examiner's interpretation is considered accurate for the sake of argument, the Applicants note that the formulation recited by the amended claims comprises particles having two distinct components: a biologically active agent, and a biocompatible polymeric matrix. As a result, the collagen particles of the dispersion disclosed by Tsunenaga do not comprise the first and second components that are required by the claims.

For the foregoing reasons, Tsunenaga fails to describe each and every element of the claims. Withdrawal of the rejection is respectfully requested.

35 U.S.C. 103(a)

Claims 20, 22-23, 25-28, and 34 were rejected under 35 U.S.C. 103(a) as obvious over Suzuki. Applicants traverse this rejection.

Amended independent claim 20 recites a method for administering a biologically active agent, comprising injecting a formulation comprising hyaluronic acid dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent weight by volume, and particles comprising a first component that is a biologically active agent and a second component that is a biocompatible polymeric matrix.

Amended independent claim 22 recites an injectable formulation comprising hyaluronic acid dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent weight by volume, and particles comprising a first component that is a biologically active agent and a second component that is a biocompatible polymeric matrix.

The administration of polymer-based drug formulations was known to be problematic in the prior art (paragraph bridging pages 2-3 of the application). Previously, excipients, surfactants, and salts had been added to reduce agglomeration or alter the particles' fluid properties (page 2 line 26 to page 3, line 2). Nevertheless, administration of the formulations through needles remained difficult (page 3, lines 3-4).

The present specification discloses for the first time that formulations comprising hyaluronic acid in the presently claimed concentration range exhibit improved injectability (Examples 3, 4, 5, and 7). Applicants have demonstrated that the use of hyaluronic acid in injectable formulations provides superior injectability compared to other polymers, including sodium alginate, dextran 70, jeffamine M-600, jeffamine ED-2001, keretan sulphate, poly-L-ornithine, xanthan gum, and gellan gum (Example 6).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: (1) the references must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the references or in the knowledge generally available to one of skill in the art, to modify the references to have all of the claim limitations; and (3) there must be a reasonable expectation of success.

Applicants submit that none of the criteria are met in the present case. Specifically, Suzuki does not disclose a formulation comprising hyaluronic acid dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent weight by volume.

Rather, Suzuki discloses microcapsules, and merely states that

> It is particularly preferred to use a microcapsule-dispersing medium which contains one or more compounds selected from the group consisting of hyaluronic acid, chondroitin sulfate, and salts thereof. The use of such a dispersion medium makes it possible to minimize irritation to the joint, which tends to occur as a result of administration (column 5, Lines 2-8).

Therefore, while Suzuki discloses the use of dispersing compounds generally, including hyaluronic acid and chondroitin sulfate, the reference neither teaches nor suggests any particular range of hyaluronic acid concentrations for use in an injectable formulation.

Nevertheless, while acknowledging that Suzuki does not disclose a formulation having the specific HA concentration range recited by the claims, the Examiner asserts it would be obvious to use "a proper amount" to maintain a suspension of microcapsules for injection. Applicants respectfully disagree.

Applicants note that, although the optimization of a concentration range is not always sufficient to establish nonobviousness over the prior art, "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." *MPEP 2144.05 II. B.*

In the present case, Applicants submit that Suzuki does not teach or suggest the present claims, because the reference fails to recognize that the parameter of hyaluronic acid concentration is a result-effective variable providing superior injectability, when present in the concentrations recited by the claims.

Indeed, and as noted above, Suzuki discloses the use of hyaluronic acid to minimize irritation to the joint, not to provide any advantages in injectability. Therefore, even if Suzuki would motivate one of ordinary skill to optimize the hyaluronic acid concentration of a formulation to minimize joint irritation after injection, Suzuki fails to recognize that HA concentration is a result-effective variable for obtaining superior injectability. Consequently, Suzuki does not provide any motivation to optimize hyaluronic acid concentrations to improve injectability of a formulation. Applicants submit the teachings of Suzuki do not provide any reasonable expectation that optimizing HA concentrations to reduce irritation would result in the presently claimed HA concentrations that improve injectability. Applicants submit the present claims are nonobvious in view of Suzuki for this reason.

Additionally, a prior art reference that discloses a range encompassing a narrower claimed range is not necessarily sufficient to establish a *prima facie* case of obviousness if "the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of the species when the

prior art broadly discloses a genus." *MPEP 2144.05 I.* The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness" *MPEP 2144.08 II.* To establish a *prima facie* case of obviousness in a genus/species context, "it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art's teachings." *MPEP 2144.08 II. A.* Office personnel should analyze the prior art in light of several factors including the size of the prior art genus, any teachings of preferred species or subgenuses, teachings of similar properties or uses compared to the claimed invention, and the predictability of the technology. *MPEP 2144.08 II. A.*

In all cases, some motivation to select the claimed subgenus must be taught by the prior art. *MPEP 2144.08 II. A. 4.(a).* Moreover, even if the Examiner determines the existence of *prima facie* obviousness, the Applicants can successfully rebut by showing that a claimed range falling within a prior art range possesses "new and unexpected results." *MPEP 2144.05 III.* A demonstration that even a single species of a claimed subgenus exhibits superior or unexpected results may be sufficient to overcome an obviousness rejection. *MPEP 2144.08 II. B.*

In light of the foregoing guidelines, Applicants respectfully submit that the range disclosed by Suzuki is so broad as to preclude a finding of obviousness, and that the prior art fails to provide any motivation to select the claimed subgenus.

Applicants reiterate that Suzuki neither discloses nor suggests any specific range of hyaluronic acid concentrations for use in an injectable formulation. Suzuki does disclose embodiments of dry powder formulations comprising specific hyaluronic acid concentrations. These dry powders, however, are not injectable formulations comprising HA dissolved in a physiological buffer, and the disclosed HA concentrations (i.e., 5.8, 7.3, and 40.2 w/w %), do not encompass the claimed range of about 0.01% to about 3% (see Examples 29-31). Therefore, Suzuki does not disclose any specific embodiment of an injectable formulation comprising a specific hyaluronic acid concentration or range of concentrations as required by the claims.

Since Suzuki does not disclose any hyaluronic acid concentration range at all for injectable formulations, the Suzuki genus is not only large, it is undefined. Applicants respectfully submit, therefore, that the teachings of Suzuki regarding hyaluronic acid are of such breadth that a finding of obviousness is precluded.

Applicants further submit that Suzuki also fails to provide any motivation to select the presently claimed HA concentration range when analyzed using any of the other factors discussed by the *MPEP*, such as the disclosure of embodiments or uses that are similar to the present invention. As noted above, Suzuki fails to disclose any specific embodiments of injectable formulations comprising hyaluronic acid, let alone formulations having concentrations within the claimed range. Nor does Suzuki teach formulations comprising hyaluronic acid for the same end use as the claimed invention. As was discussed above, Suzuki discloses that hyaluronic acid may be added to an injectable formulation to reduce irritation to a joint after injection, while the present specification discloses the use of HA to improve injectability of the formulation.

Since Suzuki fails to disclose or suggest any defined range of hyaluronic acid concentrations in an injectable formulation, it cannot provide any motivation to select the presently claimed range.

Applicants also respectfully submit that even if a presumption of obviousness exists in light of Suzuki, the specification provides evidence sufficient to rebut the presumption, by demonstrating that the claimed injectable formulations exhibit the superior result of improved injectability compared to prior art formulations.

In an obviousness analysis, "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant' s disclosure" (*MPEP 2142).* The Applicants assert that the superior injectability of formulations comprising hyaluronic acid as claimed is neither taught nor suggested by Suzuki. Specifically, Suzuki nowhere discloses or suggests anything about injectability, much less that injectable formulations comprising hyaluronic acid dissolved in a physiological buffer at a concentration of about 0.01 to about 3 percent w/v, would exhibit the superior result of improved injectability. Rather, it is the Applicants' disclosure that provides the motivation to select the claimed hyaluronic acid concentrations. Therefore, the claims are patentable in view of Suzuki for this additional reason.

Applicants respectfully submit that claims 20, 22-23, 25-28, and 34 are nonobvious in view of Suzuki for the foregoing reasons. Withdrawal of the rejection is therefore requested.

Objections

Claims 29, 33, and 36 were objected to as depending from a rejected base claim. Applicants assert that all base claims are in condition for allowance for the reasons discussed above. Therefore, claims 29, 33, and 36 are also in condition for allowance. Withdrawal of the rejection is respectfully requested.

SUMMARY

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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